ONE-STEP GEM-DIPHOSPHORYLATION OF AMIDES AND LACTAMS

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ABSTRACT

We report the extension of an easy one-step synthesis of amino *gem*-bisphosphonates through the reaction of amides and lactams with trialkylphosphites.

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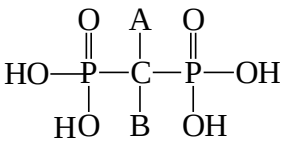
INTRODUCTION

Organic *gem*-bisphosphonates and the corresponding acids are analogues of inorganic pyrophosphates. As such, they are susceptible to find potential biomedical applications. For example, numerous *gem*-bisphosphonic acids of type **1** (Scheme 1) are currently used in the treatment of bone diseases or as antiviral compounds.[1-3]

Scheme 1



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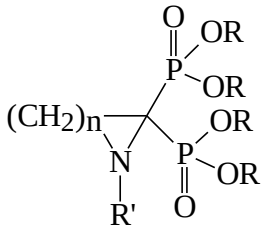


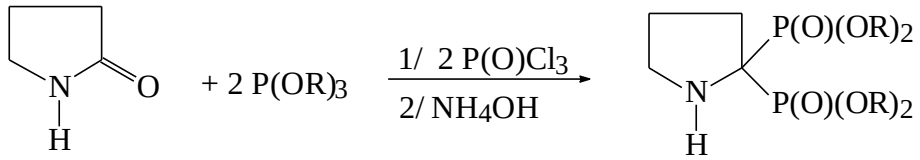
n = 3 to 5
R' = H, Me
R = H

2

Furthermore, biological applications of α-amino *gem*-bisphosphonates have also been studied, either in the aliphatic or in the alicyclic series **2** (Scheme 1).[2,4] Owing to the interest of this class of compounds[5], different synthetic routes have been reported in literature. The synthesis of azacycloalkane-2,2-bisphosphonic acids from amides was described by Plöger *et al*.[4] Gross reported the preparation of α-amino *gem*-bisphosphonates in acyclic series.[6] More recently, Zilch described a two-step synthesis of azacycloalkane-2,2-bisphosphonic acids diethyl esters.[7] Knut *et al* prepared the tetratrimethylsilyl(pyrrolidine-2,2-diyl) bisphosphonate by reaction of 4-aminobutane-1-hydroxy-1,1-bisphosphonic acid with hexamethyl disilazane.[8]

In the search of new nitrones as spin trap agents for biologically relevant radicals[9], we recently reported[10] the synthesis of the 2,2-bis(diethoxyphosphoryl)-3,4-dihydro-2*H*-pyrrole-1-oxide. This *gem*-bisphosphorylated nitrone was obtained by oxidation, with *in situ* generated dimethyldioxirane, of the tetraethyl(pyrrolidine-2,2-diyl)bisphosphonate **3** (n = 3; R = ethyl; R' = H). To synthesize **3**, we prepared the corresponding (pyrrolidine-2,2-diyl)bisphosphonic acid, but all our attempts to perform its esterification failed, even using ethylorthoformate. Finally, we prepared the tetraethyl- and tetra*iso*propyl-(pyrrolidine-2,2-diyl)bisphosphonates **3** and **4** (**4,** n = 3; R = *i*-propyl; R' = H) according to a simple synthetic scheme (Scheme 2) which was adapted from the Gross procedure.[6] This was, to our knowledge, the first reported one-step synthesis of tetraalkyl(pyrrolidine-2,2-diyl) bisphosphonates. The general experimental conditions are as follows : at = -5°C, under nitrogen, $POCl_3$ (0.44 mol.) was slowly added to a mixture of pyrrolidine-2-one (0.22 mol.) and trialkylphosphite (0.42 mol.). The reaction mixture was then stirred for five hours at room temperature and then poured over a cold aqueous solution saturated with NH_4OH. After work-up, the aminophosphonates **3** and **4** were obtained in about 50% yield (scheme 2).

Scheme 2



3: R = Et
4: R = *i*-Pr

We then started extending this reaction to other trialkyl- or triarylphosphites and lactams or amides and the results are reported in the present paper.

RESULTS and DISCUSSIONS

Gem-diphosphorylations of pyrrolidine-2-one carried out in the presence of $POCl_3$ and trialkylphosphites ($(RO)_3P$, R = Et, *i*-Pr, Bu) (scheme 3) afforded the expected *gem*-bisphosphonates in good yields (Table1). However, when we used the triphenylphosphite, no formation of *gem*-bisphosphonate was observed.

Table 1

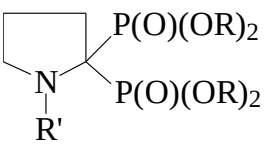
Product	Yield /% (isolated compound)	^{31}P NMR /ppm in $CDCl_3$	Ref.
(Pyrrolidine-2,2-diyl) bisphosphonic acid	18	15.0[a]	10
3	47	22.5	10
4	45	21.2	10
5	47	22.7	This work
6	0	-	This work
7	17	21.8	This work
8	0	-	This work
9	57	21.5	This work
10	56	20.0	11

a : in D_2O/Na

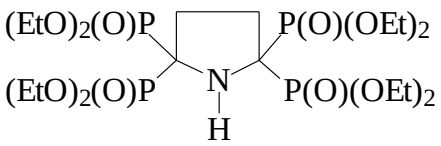
We also varied the nature of the amide or the lactam. In the presence of triethylphosphite, *N*-methyl pyrrolidine-2-one led to tetraethyl(*N*-

methylpyrrolidine-2,2-diyl) bisphosphonate **7** in 17% yield. Attempts to prepare the tetraphosphorylated compound **8** from succinimide failed. The reaction was also performed with acyclic amides: tetraethyl(*N*-benzyl-1-aminopropan-1,1-diyl) bisphosphonate **9** was obtained in 57% yield. In collaboration with us, Grimaldi[11] prepared from *N*-*tertio*butylformamide the tetraethyl *N*-*tertio*butyl aminomethylene bisphosphonate **10** in 56% yield (scheme 3). Then, this one-step bisphosphorylation reaction was successfully applied to either an alkylformamide (**10**) or a ketamide (**9**), the amide function being secondary (**9**, **10**) or tertiary (**7**) (Table 1).

Scheme 3



3: R = Et ; R' = H
4: R = *i*-Pr ; R' = H
5: R = Bu ; R' = H
6: R = Ph ; R' = H
7: R = Et ; R' = Me



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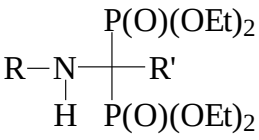
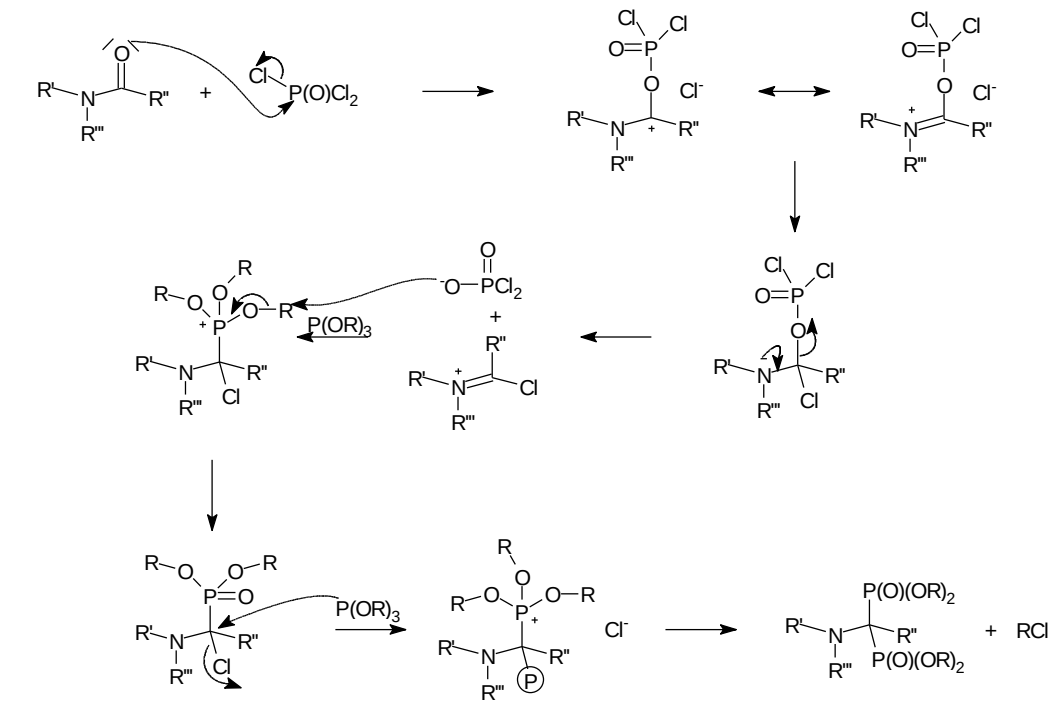


9: R = Bn ; R' = Et
10: R = *t*-Bu ; R' = H

According to our results, we can propose the reaction mechanism shown in scheme 4, involving a first step similar to that of the Vilsmeier-Haak[12] reaction. This mechanism agrees with the mechanism postulated by Gross[6] and with the lack of reaction observed with the triphenylphosphite.

Scheme 4



R''' = H, Me
Ⓟ = P(O)(OR)$_2$

CONCLUSION

In the present work, we report the extension of an easy one-step synthesis of amino *gem*-bisphosphonates. Various trialkylphosphites can be used and the reaction can be performed with amides from the alicyclic or acyclic series. Further work on this reaction will concern its extension to carbamates and to the synthesis of mixed phosphonates.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were recorded on Bruker AC 100, 200 and 400 spectrometers, and the chemical shifts (δ) in ppm referred to internal TMS or H_2O for D_2O solutions. Proton-decoupled ^{31}P-NMR spectra were recorded on a Bruker AC 100 at 40.54 MHz and the chemical shifts (δ) in ppm referred to external 85 % H_3PO_4. All *J* values are given in Hz. Elemental analyses were determined in the University of Aix-Marseille III and in the Eindhoven University of Technology. All solvents were purchased from SDS. Phosphorus acid, and trialkylphosphite were Aldrich reagents and used as purchased. Ammonia solution about 32 % was Prolabo reagent and used as purchased.

General Procedure :

Under nitrogen, phosphorus oxichloride (40 ml, 0.44 mol) was added in 1 h 15 at -5°C to amide (0.22 mol) and trialkylphosphite (0.42 mol). The reaction mixture was stirred for 5 hours at room temperature and then poured over a mixture of ice (300 g) and ammonia 32 % (300 ml). The aqueous layer was extracted with methylene chloride (4 x 100 ml) and then organic layer was concentrated to 100 ml. Water was then added (200 ml), and concentrated hydrochloric acid (37 %) was added until pH 1. The aqueous layer was washed with methylene chloride (4 x 50 ml). Except for **5**, sodium hydroxide and sodium carbonate were added until pH 10 and the aqueous layer was extracted with methylene chloride (4 x 50 ml). The organic layer was dried over sodium sulfate, filtered and removal of the solvent afforded the bisphosphonate compound.

tetrabutyl(pyrrolidine-2,2-diyl)bisphosphonate 5 : (23.2 g, yield 47 %)

Purification of **5** was performed by column chromatography (methylene chloride / ethanol 19/1 v/v) and yielded 47 % of pure compound.

^{1}H (400 MHz; C_6D_6) : δ 0.82 (t, 6H, J = 7.4, -O-CH_2-CH_2-CH_2-C$\underline{H_3}$); 0.83 (t, 6H, J = 7.4, -O-CH_2-CH_2-CH_2-C$\underline{H_3}$); 1.32 (sext., 4H, J = 7.3, -O-CH_2-CH_2-C$\underline{H_2}$-CH_3); 1.33 (sext., 4H, J = 7.5, -O-CH_2-CH_2-C$\underline{H_2}$-CH_3); 1.56 (m, 8H, -O-CH_2-C$\underline{H_2}$-CH_2-CH_3); 1.76 (quint, 2H, J = 6.9, HN-CH_2-C$\underline{H_2}$-CH_2-C); 2.49 (tt, 2H, J_{Ha-Hb} = 7.3, J_{P-H} = 17.8, HN-CH_2-$CH_{2(b)}$-C$\underline{H_{2(a)}}$-C); 2.97 (t, 2H, J = 6.5, HN-C$\underline{H_2}$-CH_2-CH_2-C); 4.22 (m, 4H, -O-C$\underline{H_2}$-CH_2-CH_2-CH_3); 4.27 (m, 4H, -O-C$\underline{H_2}$-CH_2-CH_2-CH_3); 5.30 (s, 1H, $\underline{H}$N-) ppm. **^{13}C** (100 MHz; C_6D_6) : δ 14.1 ($\underline{C}H_3$-CH_2-CH_2-CH_2-O-P); 19.4 (CH_3-$\underline{C}H_2$-CH_2-CH_2-O-P); 26.8 (t, J_{C-P} = 3.2, HN-CH_2-$\underline{C}H_2$-CH_2-C); 31.5 (t, J_{C-P} = 3.0, HN-CH_2-CH_2-$\underline{C}H_2$-C); 33.4 (t, J_{C-P} = 2.7, CH_3-CH_2-$\underline{C}H_2$-CH_2-O-P); 33.5 (t, J_{C-P} = 2.7, CH_3-CH_2-$\underline{C}H_2$-CH_2-O-P); 48.1 (t, J_{C-P} = 4.3, HN-$\underline{C}H_2$-CH_2-CH_2-C); 63.2 (t, J_{C-P} = 152.0, HN-CH_2-CH_2-CH_2-$\underline{C}$); 67.1 (t, J_{C-P} = 3.5, CH_3-CH_2-CH_2-$\underline{C}H_2$-O-P); 67.8 (t, J_{C-P} = 3.2, CH_3-CH_2-CH_2-$\underline{C}H_2$-O-P) ppm. **^{31}P** (40 MHz; $CDCl_3$) : δ 22.7 ppm. **$\underline{R_f}$** : 0.51 (methylene chloride / ethanol 19 / 1) Anal. Calcd. for $C_{20}H_{43}NO_6P_2$: C, 52.74 ; H, 9.51 ; N, 3.07 ; Found : C 52.87 ; H ; 9.45 ; N, 2.89.

tetraethyl(*N*-methyl-pyrrolidine-2,2-diyl)bisphosphonate 7 : (13.2 g, yield 17 %)

^{1}H (200 MHz; $CDCl_3$) : δ 1.34 (t, 12H, J = 7.1, -O-CH_2-C$\underline{H_3}$); 1.84 (quint, 2H, J = 6.6, HN-CH_2-C$\underline{H_2}$-CH_2-C); 2.43 (m, 2H, N-CH_2-CH_2-C$\underline{H_2}$-C); 2.79 (t, 3H, J = 1.7, C$\underline{H_3}$-N); 2.84 (t, 2H, J = 6.6, N-C$\underline{H_2}$-CH_2-CH_2-C); 4.21 (m, 8H, -O-C$\underline{H_2}$-CH_3) ppm. **^{13}C** (50 MHz; $CDCl_3$) : δ 16.1 ($\underline{C}H_3$-CH_2-O-P-); 23.6 (N-CH_2-$\underline{C}H_2$-CH_2-C); 32.2 (t, J_{C-P} = 4.6, N-CH_2-CH_2-$\underline{C}H_2$-C); 37.3 ($\underline{C}H_3$-N); 55.3 (t, J_{C-P} = 4.7, N-$\underline{C}H_2$-CH_2-CH_2-C); 62.2 (t, J_{C-P} = 4.6, CH_3-$\underline{C}H_2$-O-P); 64.2 (t, J_{C-P} = 153.0, N-CH_2-CH_2-CH_2-$\underline{C}$) ppm. **^{31}P** (40 MHz; $CDCl_3$) : δ 21.8 ppm. **$\underline{R_f}$** : 0.61 (methylene chloride / ethanol 19 / 1).

tetraethyl(*N*-benzyl-1-aminopropan-1,1-diyl)bisphosphonate 9 : (50.5 g, yield 57 %)

^{1}H (400 MHz; $CDCl_3$) : δ 1.12 (t, 3H, J = 7.5, $C\underline{H}_3$-CH_2-C-N); 1.31 (t, 6H, J = 7.1, -O-CH_2-$C\underline{H}_3$); 1.32 (t, 6H, J = 7.1, -O-CH_2-$C\underline{H}_3$); 2.13 (tq, 2H, J_{H-H} = 7.5, J_{P-H} = 15.0, CH_3-$C\underline{H}_2$-C-N); 4.00 (s, 1H, C-N$\underline{H}$); 4.11 (m, 2H, Ph-$C\underline{H}_2$-N-); 4.21 (m, 8H, -O-$C\underline{H}_2$-CH_3); 7.24 (m, 5H, aromatics) ppm. **^{13}C** (100 MHz; $CDCl_3$) : δ 8.5 (t, J_{C-P} = 6.5, $\underline{C}H_3$-CH_2-C-N); 16.5 ($\underline{C}H_3$-CH_2-O-P-); 23.5 (CH_3-$\underline{C}H_2$-C-N); 47.9 (t, J_{C-P} = 6.5, Ph-$\underline{C}H_2$-N-); 62.8 (t, J_{C-P} = 140.1, -CH_2-$\underline{C}$-N); 62.8 (t, J_{C-P} = 3.1, CH_3-$\underline{C}H_2$-O-P); 63.1 (t, J_{C-P} = 3.2, CH_3-$\underline{C}H_2$-O-P); 127.0 (aromatic para); 128.2 (aromatic ortho); 128.3 (aromatic meta); 140.5 (quaternary aromatic) ppm. **^{31}P** (40 MHz; $CDCl_3$) : δ 21.5 ppm.

tetraethyl (*N-tertio*butylaminomethylene)bisphosphonate 10[11] : (28.8 g, yield 56 %)

^{1}H (200 MHz; $CDCl_3$) : δ 1.12 (s, 9H, $C\underline{H}_3$-C); 1.35 (t, 12H, J_{H-H} = 6.0, $C\underline{H}_3$-CH_2); 2.77 (m, 1H, C$\underline{H}$-P), 4.1-4.3 (m, 8H, $C\underline{H}_2$) ppm. **^{13}C** (50 MHz; $CDCl_3$) : δ 16.1 (m, $\underline{C}H_3$-CH_2); 29.2 ($\underline{C}H_3$-C); 48.9 (t, J_{C-P} = 148.5, $\underline{C}$H-P); 51.7 (t, J_{C-P} = 10.5, $\underline{C}$-N); 62.5 (d, J_{C-P} = 4.0, $\underline{C}H_2$) ; 62.6 (d, J_{C-P} = 3.5, $\underline{C}H_2$) ; 63.1 (d, J_{C-P} = 3.2); 63,2 (d, J_{C-P} = 3.9) ppm. **^{31}P** (40 MHz; $CDCl_3$) : δ 20.0 ppm. Anal. Calcd. for $C_{13}H_{31}NO_6P_2$: C, 43.45 ; H, 8.70 ; N, 3.90 ; Found : C , 43.12 ; H ; 8.86 ; N, 3.58.

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